PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR VIREAD (TENOFOVIR DISOPROXIL FUMARATE)

This is a summary of the risk management plan (RMP) for Viread. The RMP details important risks of Viread, how these risks can be minimized, and how more information will be obtained about Viread's risks and uncertainties (missing information).

Viread's summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how Viread should be used.

This summary of the RMP for Viread should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Viread's RMP.

I. The Medicine and What is it Used for

Viread is authorized for the treatment of patients aged 2 years and above infected with human immunodeficiency virus type 1 (HIV-1), a virus that causes acquired immune deficiency syndrome (AIDS). Viread is used in combination with other HIV medicines. In children and adolescents its use is only for those who cannot be treated with other first-line nucleos(t)ide reverse transcriptase inhibitors (NRTI) (see Viread SmPC for the full indication).

Viread is also used to treat chronic (long-term) hepatitis B virus (HBV) infection in patients aged 2 years and above with liver damage whose liver is still working properly (compensated liver disease). In adults, it can also be used for those patients with liver damage whose liver is not working properly (decompensated liver disease) and those patients who do not respond to treatment with lamivudine (another medicine used for the treatment of chronic HBV infection) (see Viread SmPC for the full indication).

Viread contains tenofovir disoproxil fumarate (TDF) as the active substance and it is given orally.

Further information about the evaluation of Viread's benefits can be found in Viread's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/viread

II. Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of Viread, together with measures to minimize such risks and the proposed studies for learning more about Viread's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the public (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In the case of Viread, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed including periodic safety update report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Viread is not yet available, it is listed under 'missing information' below.

II.A. List of important risks and missing information

Important risks of Viread are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Viread. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table Part VI.1. List of Important Risks and Missing Information

Important Identified Risks	Renal toxicity
	Bone events due to proximal renal tubulopathy/loss of bone mineral density
Important Potential Risks	None
Missing Information	Safety in pregnancy and lactation
	Safety in patients with renal impairment

II.B. Summary of Important Risks

Viread has been assigned the legal status of a medicine subject to medical prescription in the European Union (EU), whereby Viread therapy should be initiated by a doctor experienced in the management of HIV infection and/or treatment of chronic hepatitis B (as described in section 4.2 of the SmPC).

Table Part VI.2. Summary of Important Risk(s) and Missing Information

Important Identified Risk	**Renal Toxicity**
Evidence for linking the risk to the medicine	Renal failure, renal impairment, elevated creatinine in blood, low levels of phosphate in blood (hypophosphatemia) and damage to kidney tubule cells (proximal renal tubulopathy [including Fanconi syndrome]) have been reported with the use of TDF in clinical trials and in the postmarketing setting.
Risk factors and risk groups	Risk factors for renal events include advanced HIV disease (low CD4 [antigenic marker on helper/inducer T cells] count at the start of treatment), low weight, older age, renal impairment before starting therapy, use of other medicines that are damaging to kidneys, high blood pressure, and also being infected with hepatitis C virus.
Risk minimization measure(s)	Routine risk communication: SmPC sections 4.2, 4.4, 4.5 and 4.8 PL sections 2 and 4 Routine risk minimization activities recommending specific clinical measures to address the risk: SmPC section 4.4: Recommendation for renal function monitoring and guidance on when to interrupt or discontinue TDF SmPC section 4.4: Guidance that, for pediatric patients, a multidisciplinary approach is recommended to adequately weigh the benefit/risk balance of treatment, decide the appropriate monitoring and consider the need for supplementation.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Monitoring of reversibility of renal tubulopathy in clinical trials See Section 0 of this summary for an overview of the post-authorization development plan.

Important Identified Risk	**Bone Events Due to Proximal Renal Tubulopathy/Loss of Bone Mineral Density**
Evidence for linking the risk to the medicine	In the postmarketing setting, there have been rare occurrences of damage to kidney tubule cells associated with TDF therapy leading to bone softening (osteomalacia) with bone pain and sometimes resulting in fractures. Thinning of bones (decreases in bone mineral density [BMD]) has been observed in patients treated with TDF during clinical trials. However, the clinical significance is unknown as no increase in fracture rates has been observed.
Risk factors and risk groups	HIV infection is known to be associated with bone disease. Reduced BMD and impaired calcium metabolism is known to be associated with cirrhosis of the liver. A number of small studies have shown that people with liver cirrhosis related to hepatitis B or hepatitis C virus infection have reduced BMD and reductions in BMD are correlated with the severity of liver disease.
Risk minimization measure(s)	Routine risk communication: SmPC sections 4.4, 4.8 and 5.1 PL sections 2 and 4 Routine risk minimization activities recommending specific clinical measures to address the risk: SmPC section 4.4: Guidance on action to be taken if bone abnormalities are suspected SmPC section 4.4: Guidance that, for pediatric patients, a multidisciplinary approach is recommended to adequately weigh the benefit/risk balance of treatment, decide the appropriate monitoring and consider the need for supplementation
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** See Section 0 of this summary for an overview of the post-authorization development plan.
Missing Information	**Safety in Pregnancy and Lactation**
Risk Minimization Measure(s)	Routine risk communication: SmPC sections 4.6 and 5.3 PL section 2
Additional Pharmacovigilance Activities	Additional pharmacovigilance activities: Antiretroviral Pregnancy Registry See Section 0 of this summary for an overview of the post-authorization development plan.
Missing Information	**Safety in Patients with Renal Impairment**
Risk minimization measure(s)	Routine risk communication: SmPC sections 4.2, 4.4, 4.8 and 5.2 PL sections 2 Routine risk minimization activities recommending specific clinical measures to address the risk: SmPC section 4.4: Recommendation for dosage adjustment and close monitoring of renal function if TDF is used in an adult patient with creatinine clearance < 50 ml/min (SmPCs for Viread 245 mg film-coated tablets and Viread 33 mg/g granules). The use of TDF is not recommended in pediatric patients with renal impairment.

II.C. Post-authorization Development Plan

II.C.1. Studies which are Conditions of the Marketing Authorization

There are no studies which are conditions of the marketing authorization or specific obligation of Viread.

II.C.2. Other Studies in Post-Authorization Development Plan

Table Part VI.3. Other Studies in Post-Authorization Development Plan

Short Study Name	Purpose of the Study
Antiretroviral Pregnancy Registry	*Objectives:* To collect information on the risk of birth defects in patients exposed to TDF during pregnancy *Safety concern(s) addressed:* Missing information: Safety in pregnancy and lactation
Monitoring of reversibility of renal tubulopathy in clinical trials	To collect information on the reversibility of renal tubulopathy following the discontinuation of TDF in adult and pediatric patients